

REMARKS

This Response, filed in reply to the Office Action dated October 3, 2008, is believed to be fully responsive to each point of objection and rejection raised therein. Accordingly, favorable reconsideration on the merits is respectfully requested.

Claims 1-6 and 25-27 are rejected. Consideration of the remarks herein is respectfully requested.

Information Disclosure Statement

Applicants thank the Examiner for returning and signed and initialed copy of the PTO Form SB/08 that accompanied the Information Disclosure Statement filed June 19, 2008, indicating consideration of the JP 2002-176880 and JP 2001-520009 references.

Withdrawn Objections and Rejections

1. Applicants thank the Examiner for withdrawal of the objection to the drawings.
2. Applicants thank the Examiner for withdrawal of the rejection of Claims 1-6 and 24 under 35 U.S.C. 102(e), as allegedly being anticipated by Sang *et al.*
3. Applicants thank the Examiner for withdrawal of the *provisional* obviousness-type double patenting rejection of Claims 1-6 and 24 over copending U.S. Patent Application No. 10/569,268.

Claims 25-27 are Patentable Under 35 U.S.C. § 102

On page 3 of the Office Action, the Examiner maintains the rejection of Claims 25-27 under 35 U.S.C. 102(e) as being anticipated by Ransohoff *et al.* (U.S. Patent Application Pregrant Publication 2003/0176660), essentially for reasons of record. In response to Applicants' previous arguments that the instantly claimed *product* is not anticipated by Ransohoff *et al.* at least by virtue of the presence of MMLV-derived vector sequences in the claimed transgenic avian, the Examiner appears to maintain the rejection on the basis that the method steps of Claim 1, particularly the steps of mating G0 transgenic chimeras to wild-type birds, does not necessarily result in germline transduction, and thus the eggs of Claims 25-27 need not actually contain the transgene nor the MMLV-derived vector sequences.

Applicants disagree, and traverse the rejection, respectfully, in view of the following remarks.

Initially, Applicants note that Claim 1, from which Claims 25-27 directly depend, recites a “*transgenic* bird ... which is obtained as a G1 *transgenic* bird or an offspring thereof.” Thus, contrary to the Examiner's position, Claim 1 is not directed to the offspring from G0 transgenic chimeras that do not contain the transgene, which are, *by definition*, not transgenic birds. Rather, the transgenic bird of Claim 1, by virtue of being a **G1 transgenic** bird (or transgenic offspring thereof), logically would produce eggs containing the transgene and the MMLV-derived vector sequences, because the production of **G1 transgenic** birds involves germline transduction of the transgene.

Thus, maintenance of the rejection requires ignoring the recitation in Claim 1 that the claimed bird is a “transgenic bird” and that it is a “G1 transgenic bird or an offspring thereof.” Pursuant to M.P.E.P. § 2134.03, “[a]ll words in a claim must be considered in judging the patentability of that claim against the prior art.” Given the plain and ordinary meaning of the terms “transgenic” and “transgene,” Applicants respectfully submit that one of ordinary skill in the art would not understand birds which do not contain a transgene, to be “transgenic birds.”

Applicants again note that “[a] claim is anticipated *only* if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.” (Emphasis added.) *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir 1987). In the context of anticipation of product-by-process claims, a claimed product may *only* be anticipated by a prior art reference that discloses *the same* product. For at least the above reason, the process steps of Claim 1 impart structural differences upon the claimed product vis-à-vis the product of Ransohoff *et al.* Accordingly, the claimed products of Claims 25-27 are *not* the same as that disclosed by Ransohoff *et al.*, as is required to maintain a finding of anticipation in the instant case. Accordingly, Ransohoff *et al.* do not anticipate the claims.

Withdrawal of the rejection is respectfully requested.

Claims 1, 5-15 and 18 are Patentable Under 35 U.S.C. § 103

On page 5 of the Office Action, the Examiner rejects Claims 1, 5-15 and 18 under 35 U.S.C. 103(a) as being unpatentable over Sang *et al.* (U.S. Patent Application Pregrant

Publication No. 2005/0273872), as evidenced by Kamachi *et al.* (*Development*, 1998, 125:2521-2532), in view of Rapp *et al.* (U.S. Patent Application Pregrant Publication No. 2002/0108132).

In making the rejection, the Examiner indicates that the rejected claims are interpreted as product-by-process claims, and that the structural elements of the transgenic chicken, such as the presence of a replication defective retroviral vector encoding a desired protein, are relevant to patentability.

Turning to Sang *et al.*, the Examiner contends that Sang *et al.* disclose the production of transgenic avians, and the expression of transgene encoded protein within an avian egg, citing the Abstract. Although the Examiner alleges that Sang *et al.* disclose the use of VSV-G pseudotyped lentiviral vectors to produce G0 transgenic chickens, the Examiner expressly acknowledges that Sang *et al.* do not describe the production of transgenic chickens using a retroviral vector derived from Moloney murine leukemia virus. In an attempt to rectify the deficiencies of Sang *et al.*, the Examiner cites to Rapp *et al.*, who allegedly disclose transgenic chickens transformed with recombinant retroviral expression vectors, including a Moloney murine leukemia virus-derived vector. The Examiner takes the position that one of ordinary skill in the art would readily have incorporated the retroviral vector of Rapp *et al.* in the method of Sang *et al.* “as a matter of design choice,” alleging that such a modification of the method of Sang *et al.* amounts only to combining prior art elements according to known methods to yield predictable results.

Applicants disagree, and traverse the rejection, respectfully, in view of the following remarks.

First, Applicants respectfully point out that, even assuming *arguendo* that one of ordinary skill in the art would have possessed sufficient motivation to combine Rapp *et al.* and Sang *et al.* in the manner asserted in the rejection, they nevertheless would not arrive at the presently claimed invention. Specifically, as acknowledged by the Examiner on page 6 of the Office Action, Sang *et al.* disclose inoculation of chicken embryos at any of stages X-XIII, *i.e.*, blastodermic stages. In contrast, the transgenic bird of the instantly claimed invention is produced by microinjection of a MMLV-derived vector “at a stage except for and after the blastodermic stage just after egg laying,” *i.e.*, just after egg laying and *after the blastodermic stage*. Applicants respectfully point out that this specific *post*-blastodermic inoculation imparts distinct and nonobvious structural characteristics to the resulting G1 transgenic bird or transgenic progeny thereof, or egg thereof. Specifically, by performing microinjection of the claimed MMLV-derived vector *after the blastodermic stage*, just after egg laying, transgene expression is not subject to gene silencing, thus preventing down-regulation of expression of the transgene. As a consequence of microinjection at this specific developmental stage, the transgenic bird, and egg thereof, of the present invention exhibits unexpectedly superior transgene expression, *i.e.*, the claimed process steps impart an entirely unexpected and non-obvious structural difference vis-à-vis the transgenic birds of Rapp *et al.* and Sang *et al.* It is well-settled that a finding of obviousness can be rebutted by a demonstration of unpredicted or unexpected results.

As evidence of such, Applicants respectfully refer the Examiner to Tables 2 and 3 in Example 9 of the present specification, which demonstrate that the concentration of exogenous antibody in the blood of a G2-transgenic bird of the present invention is 0.35-0.75 mg/ml.

Further, Table 4 demonstrates that 0.57 mg/ml, and 0.33 mg/ml, of exogenous antibody is present in the bird's egg albumin and yolk, respectively. Notably, a further unexpected property of the claimed transgenic birds, as demonstrated in Tables 2 and 3, is that transgene silencing is successfully inhibited in future generations, such as G2 transgenic offspring. In contrast, the level of transgene expression by the methods of Sang *et al.* and Rapp *et al.* is substantially reduced in comparison to the method of the present invention. For example, Sang *et al.* disclose in paragraph [0098], and in Figure 4b, that only about 50 picograms of transgene encoded protein, namely beta-galactosidase, is present in 1 microgram of total tissue protein, *i.e.*, about 50µg per gram of total tissue. However, even assuming *arguendo* for comparative purposes that 1 gram of tissue protein of Sang *et al.* is equivalent to 1 ml of blood from the G2 transgenic bird in instant Example 9 (when in actuality 1 ml of blood contains less than 100% w/v of protein), the method of Sang *et al.* would only produce 50µg of protein, whereas the instantly claimed method, as evidenced in Tables 2 and 3, produces between 350-750 µg. In addition, Rapp *et al.* disclose in Example 4 that exogenous antibody production in the blood of the transgenic bird is merely to a level of 2ng/ml, several thousand-fold lower than that achieved by the present invention. In view of such unexpectedly superior transgene expression vis-à-vis the closest applied references, the instant claims are not rendered obvious over Rapp *et al.* and Sang *et al.*, taken alone or in combination.

Further, and independent of the above arguments, Applicants respectfully submit that one of ordinary skill in the art would be strongly discouraged from incorporating the retroviral vector of Rapp *et al.* into the method of Sang *et al.*, because Sang *et al.* state that the use of a delivery

vector derived from Moloney murine leukemia virus during development leads to gene silencing, and “very low expression of the transgene,” and that “it is therefore essential that any viral vector used for production of transgenic birds does not exhibit gene silencing.” See paragraph [0016]. Thus, Sang *et al.* expressly teaches away from the combination asserted in the rejection. It is well-settled that a reference teaches away when a person of ordinary skill in the art, upon reading it, would be discouraged from following the path set out in the reference, or would be led in a path divergent from the path taken by the inventor. See *Monarch Knitting Mach. Corp v. Sulzer Morat GmbH*, 139 F.3d, 877, 45 USPQ2d 1977 (Fed. Cir. 1998); *Para-Ordnance Mfg. v. SGS Importers Int’l Inc.*, 73 F.3d1085, 37 USPQ2d 1237 (Fed. Cir. 1995); and *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). Clearly, one of ordinary skill in the art, reading Sang *et al.*, would be discouraged from employing a MMLV-derived vector during development, due to the express indication that such results in gene silencing. Although the Examiner appears to take the position that this teaching-away by Sang *et al.* refers to gene silencing during mouse embryogenesis, and that such is not extendible to avians, in view of “subsequent publications with regard to using Moloney murine leukemia virus as an expression vector in chimeric or transgenic birds,” Applicants respectfully disagree. First, an obvious inquiry is determined based on the knowledge of those of ordinary skill in the art *at the time the invention was made*. See M.P.E.P. § 2141.01. Thus, reliance on subsequent publications, available after the time of the present invention, is clearly improper. Further, notwithstanding the impropriety and complete lack of evidentiary support for the contention that subsequent publications provide further motivation to arrive at the presently claimed invention, the Examiner is respectfully reminded

that, at the time of the invention, the art recognized that regulation of gene expression, including gene silencing, during early embryogenesis is highly conserved amongst vertebrates, and as such, one of ordinary skill in the art, at the time of the invention, would have considered that MMLV-derived vectors would also result in transgene silencing in avians.

For the above reasons, Applicants respectfully submit that the cited references do not render obvious Applicants' claimed invention.

Withdrawal of the rejection is respectfully requested.

Obviousness Type Double Patenting

On page 8 of the Office Action, the Examiner *provisionally* rejects Claims 1-6 and 24-27 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1, 41, 44-47 and 49-56 of copending U.S. Patent Application No. 10/523,191.

In response, Applicants respectfully point out that U.S. Patent Application No. 10/523,191 is abandoned as of September 17, 2008, mooted the rejection.

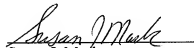
Withdrawal of this rejection is respectfully requested.

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

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23373

CUSTOMER NUMBER

Date: March 3, 2009